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The Effect of Metabolic Syndrome on the Occurrence of Restenosis After Carotid Endarterectomy

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Objectives

The metabolic syndrome (MetS) is a cluster of risk factors for cardiovascular disease. The effect of MetS on clinical outcome in patients with cerebrovascular disease remains largely unknown because conflicting results have been published. This study aimed to determine the influence of MetS on the occurrence of restenosis after carotid endarterectomy (CEA).

Methods

All patients who underwent CEA between June 2003 and December 2014 in two tertiary academic referral centres in The Netherlands were included. MetS was defined if three or more of the following criteria were present: hypertension, obesity, high fasting serum blood glucose, high serum triglycerides, or low serum high density lipoprotein cholesterol. The primary outcome measure was the occurrence of ipsilateral restenosis after index surgery. The secondary outcome measure was (all cause) mortality during follow up. For the primary analysis, missing data were multiply imputed using multivariable imputation by chained equations. A Cox proportional hazards model was used to perform an adjusted analysis on the multiply imputed data sets.

Results

A total of 1668 CEA procedures (in 1577 patients) were performed. The presence or absence of MetS could not be determined in 263 patients because of missing data. There was no significant difference in freedom from restenosis in the MetS group vs. the no-MetS group (hazard ratio [HR], 1.10; 95% confidence interval [CI] 0.98-1.23; *p* = .10) or in all cause mortality (HR 1.20; 95% CI 0.94-1.54; *p* = .14).

Conclusion

This study shows that MetS does not predict restenosis after CEA. Also, the presence of MetS did not influence patient survival negatively.

**Keywords:** Metabolic syndrome; Carotid endarterectomy; Restenosis; Survival; Surveillance

## What this paper adds

This study presents the largest published cohort so far on the effect of metabolic syndrome (MetS) on restenosis and death after carotid endarterectomy. Data from previous studies are conflicting regarding an effect of MetS on the restenosis rate. This study shows that MetS has little clinical relevance in advanced atherosclerotic carotid disease with regard to restenosis and death after surgery. MetS is useful in screening and detection of the early stages of atherosclerosis but has no role in the outcome or management of severe atherosclerosis of the carotid artery requiring surgical treatment.

## Introduction

Metabolic syndrome (MetS) is a condition characterised by a cluster of cardiovascular risk factors, including hypertension, obesity, high fasting serum blood glucose, high triglycerides, and low high density lipoprotein (HDL). Patients with MetS have a twofold increased risk of developing cardiovascular disease and a 1.5 fold increased risk of all cause mortality compared with patients without MetS.<sup>1</sup> MetS is associated with platelet and endothelial dysfunction and thereby constitutes a pro-thrombotic environment.<sup>2</sup> In haemodialysis patients, MetS has a negative effect on arteriovenous access patency. Although primary patency rates are comparable, secondary patency rates are significantly lower in patients with MetS compared with no MetS.<sup>3</sup> In peripheral artery disease, patients treated endovascularly for superficial femoral artery lesions had similar patency rates between the MetS and no-MetS groups. However, a worse symptomatic and functional outcome was noted in the MetS group, compared with the no-MetS group.<sup>4</sup> The effect of MetS on clinical outcome in patients with cerebrovascular disease is little known. A recent study found that the presence of MetS had no negative effect on short and long term complications and overall survival after carotid endarterectomy (CEA).<sup>5</sup> This is in contrast to previous studies showing that MetS patients after CEA and carotid artery stenting are at a greater risk of peri-operative and long term morbidity (ischaemic stroke, myocardial infarction, and major adverse events) compared with patients without MetS.<sup>6,7</sup> In addition, contradictory results have been published with respect to restenosis after CEA in MetS patients. Increased rates of restenosis<sup>7,8</sup> and comparable rates of restenosis<sup>6</sup> after CEA have both been described between MetS and no-MetS patients. The aim of the present study was to further elucidate the meaning of MetS in clinical practice and follow up strategy after CEA. Therefore, the influence of MetS was analysed on occurrence of restenosis and patient survival after CEA.

## Methods

### Study design

Patients treated by CEA between June 2003 and December 2014 in two Dutch academic tertiary referral centres, University Medical Centre Groningen (UMCG) and University Medical Centre Utrecht (UMCU), were included. All patients were prospectively recorded in two separate vascular registries. The purpose of these registries is scientific research and the obligatory clinical auditing in the Netherlands.<sup>5,9</sup> Both registries contain patients with symptomatic and asymptomatic carotid stenosis who subsequently underwent CEA.

After inclusion, baseline characteristics were obtained from questionnaires and patient medical records. Data included cardiovascular risk factors, history of cardiovascular disease, and medication use. Blood samples were taken pre-operatively for various laboratory tests (i.e., creatinine, glucose, triglycerides, high density lipoprotein cholesterol, and total cholesterol). All patients underwent follow up for restenosis of the ipsilateral carotid artery and stenosis of the contralateral carotid artery by duplex ultrasound examination starting three months post-operatively and yearly thereafter. Outcome measures were double checked using the patient records and by contacting the general practitioner. Institutional Review Board approval was obtained (METc 2015/368). Because retrospective patient file research does not fall under the scope of the Dutch Medical Research Involving Human Subjects act, informed consent was not required. All patient related data were processed anonymously and stored electronically.

### Procedure

Details of patient assessment and surgical procedure have been published previously.<sup>5,10,11</sup> In short, patients received antiplatelet medication with acetylsalicylic acid (100 mg/d) or clopidogrel (75 mg/d) pre-operatively, except for patients who were already on anticoagulants. Patients received 5000 IU of heparin *i.v.* before the carotid artery was clamped.

Intra-operative monitoring was performed using electroencephalography and transcranial Doppler. When significant changes in electroencephalography and/or transcranial Doppler occurred, intra-operative shunting was performed (Javid Carotid Shunt; Bard, Tempe, AZ, USA).<sup>12</sup> The longitudinal arteriotomy was closed with autologous vein or bovine patch (XenoSure Biologic Vascular Patch; LeMaitre, Burlington, MA, USA) or synthetic patch (AlboSure Polyester Vascular Patch; LeMaitre). The arteriotomy was closed primarily with a running suture in selected cases (internal carotid artery > 5 mm in diameter). Post-operatively, antiplatelet or anticoagulant therapy was continued for

life.

## Definitions

MetS was defined if three or more of the following criteria were present: hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of antihypertensive medication), serum triglycerides >1.69 mmol/L (>150 mg/dL), serum HDL cholesterol <1.03 mmol/L (<40 mg/dL) in men or <1.29 mmol/L (<50 mg/dL) in women, fasting serum blood glucose >6.1 mmol/L (>110 mg/dL) or use of diabetic medication, and body mass index >30 kg/m<sup>2</sup>.<sup>5-8,13</sup> All measurements were performed during the outpatient visit or at time of admission for the CEA procedure. To compare outcomes with previous studies on MetS and CEA outcome, the same cutoff scores and tools were chosen, which included using the body mass index rather than waist circumference.

Because no fasting glucose measurements were available for patients within the Athero-Express Biobank (UMCU), the following composite definition was used: patients with use of antidiabetic medication or previously diagnosed with diabetes mellitus by a medical doctor according to the definition of the World Health Organisation/International Diabetes Federation ('Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced').<sup>14,15</sup>

A symptomatic carotid stenosis was defined as an ipsilateral transient ischaemic attack, cerebrovascular accident, or ocular symptoms during the three months before the index operation. Asymptomatic stenosis was defined as an asymptomatic ICA stenosis >50% (according to the European Society for Vascular Surgery [ESVS] guideline).<sup>16</sup> A small group of patients had surgery for a symptomatic carotid stenosis based on vertebrobasilar insufficiency or haemodynamic impairment causing watershed transient ischaemic attack/cerebrovascular accident.

Impaired kidney function was defined as an estimated glomerular filtration rate <90 mL/min/1.73 m<sup>2</sup> calculated using the Modification of Diet in Renal Disease Study equation.<sup>17</sup> Pulmonary disease was defined as a history of chronic obstructive pulmonary disease, pulmonary fibrosis, asthmatic bronchitis, asthma, sarcoidosis, or use of respiratory medication. History of coronary artery disease was defined as a history of angina pectoris, myocardial infarction, coronary artery disease, coronary artery bypass grafting, or percutaneous coronary intervention. Use of antithrombotics was defined as pre-operative use of anticoagulants or antiplatelet therapy.

## Outcome measures

The primary outcome measure was the occurrence of ipsilateral restenosis after the index procedure. Restenosis was defined as a stenosis ≥50%. The degree of stenosis was based on the measured peak systolic velocity (PSV), end diastolic velocity (EDV), and their ratios in the internal carotid artery (ICA) and common carotid artery (CCA) using thresholds derived from criteria formulated by Bluth *et al.*<sup>18</sup> The thresholds used for a ≥50% stenosis were an ICA PSV ≥ 125 cm/s, an ICA/CCA PSV ratio ≥ 2.0 and an ICA/CCA EDV ratio ≥ 8.0. Occlusion was defined as the absence of flow by duplex ultrasound and confirmed by computed tomography angiography or magnetic resonance angiography. The secondary outcome measure was (all cause) mortality during follow up. Cause of death was not reliably available for most patients.

## Statistical analysis

This study reported according to the STROBE guidelines, as stated in strobe-statement.org. Categorical variables are presented as numbers and percentages. Differences were tested with the Pearson chi-square or Fisher exact test. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables and as median with interquartile range (25th and 75th percentile) for skewed variables. Differences were tested with the Student two tailed *t* test for normally distributed data or the Mann-Whitney *U* test for skewed data. These were all complete case analyses.

For the primary analysis, missing data were multiply imputed using multivariable imputation by chained equations.<sup>19</sup> The number of imputations was determined according to the two stage procedure as recommended by Von Hippel.<sup>20</sup> A total of 30 different imputed data sets was constructed. Parameters, with their standard errors, were estimated with Cox regression applied to each data set separately, and pooled using Rubin's rule.<sup>21</sup> Apart from the variables of interest, the Nelson-Aalen estimator was calculated and also included in the imputation algorithm because it leads to the lowest bias and highest power in survival analyses.<sup>22</sup> Kaplan-Meier analyses were used to estimate freedom from restenosis and patient survival, and the log rank test was used to compare differences in freedom from restenosis and survival between the no-MetS and MetS group. Cox proportional hazards regression analyses were used to determine the effect of MetS on freedom from restenosis and patient survival. A Cox proportional hazards model including sex (male/female), age (y), pre-operative ipsilateral symptoms (yes/no), ipsilateral stenosis at the time of carotid endarterectomy (0-50%, 50-70%, >70%), current smoking status (yes/no), kidney function (normal/impaired), history coronary artery disease (yes/no), history of cerebrovascular disease (yes/no), and current use of antithrombotics (yes/no) was used to perform an adjusted analysis. These variables were selected based on literature<sup>6,8</sup> and subject matter knowledge. The proportional hazard assumption was evaluated using log-log plots, the goodness of fit testing approach, and time dependent covariates.

Two tailed *p* values were used throughout, and significance was set at *p* < .05. Statistical analyses were performed in R 3.5.0 software<sup>23</sup> using the *mice*,<sup>24</sup> *survival*,<sup>25</sup> and *survminer*<sup>26</sup> packages.

## Results

Baseline characteristics

A total of 1668 CEA procedures (in 1577 patients) were performed, and 1172 (70.3%) of the patients were men. The mean age of the patients was 69.2 ± 9.3 y, 574 patients (34%) met the MetS definition, and 831 (49.8%) did not. The presence or absence of MetS could not be reliably determined in 263 patients because of missing data. Baseline characteristics were stratified by MetS presence and summarised in [Table 1](#) (complete case analysis). The distribution of MetS components between the two cohorts is presented in [Table 2](#). For the 263 patients for whom the presence or absence of MetS could not be determined because of missing data, multivariable imputation was applied. The missing data consisted mainly of serum triglycerides (298 data records missing) and HDL cholesterol (305 data records missing). Complete case analysis showed significant differences in current smoking status ( $p = .016$ ), the pre-operative use of anticoagulant/antiplatelet medication ( $p = .005$ ), and history of coronary artery disease ( $p < .001$ ) between the groups.

**Table 1** Demographics and comorbidities of patients with or without metabolic syndrome (MetS) studied for occurrence of restenosis after carotid endarterectomy

alt-text: Table 1					
Characteristic	All patients* ( <i>n</i> = 1668)	Missing <i>n</i> (%)	No-MetS ( <i>n</i> = 831)	MetS ( <i>n</i> = 574)	<i>p</i>
Male sex – <i>n</i> (%)	1172 (70.3)	0	588/831 (70.8)	403/574 (70.2)	.82
Mean age ± SD – y	69.2 ± 9.3	0	69.2 ± 9.4	68.7 ± 9.3	.30
Symptomatic carotid stenosis – <i>n</i> (%)	1217 (73.0)	0	623/831 (75.0)	419/574 (73.0)	.41
Current smoker – <i>n</i> (%)	615 (36.9)	19 (1.1)	345/826 (41.8)	199/563 (35.3)	.02
Hypertension – <i>n</i> (%)	1487 (89.1)	23 (1.4)	679/817 (83.1)	559/572 (97.7)	<.001
Impaired kidney function – <i>n</i> (%)	1301 (78.0)	100 (6.0)	639/784 (81.5)	455/548 (83.0)	.48
Pulmonary disease – <i>n</i> (%)	247 (14.8)	0	132/831 (15.9)	78/574 (13.6)	.24
History of coronary artery disease – <i>n</i> (%)	597 (35.8)	3 (0.2)	253/830 (30.5)	252/572 (44.1)	<.001
History of TIA/CVA – <i>n</i> (%)	867 (52.0)	0	410/831 (49.3)	274/574 (47.7)	.56
History of atrial fibrillation – <i>n</i> (%)	51 (3.1)	0	27/831 (3.2)	24/574 (4.2)	.36
Diabetes mellitus – <i>n</i> (%)	469 (28.1)	3 (0.2)	90/830 (10.8)	318/572 (55.6)	<.001
Use of antithrombotics – <i>n</i> (%)	678 (40.6)	4 (0.2)	352/828 (42.5)	287/573 (50.1)	.01
Patch used in closure of arteriotomy – <i>n</i> (%)	1573 (94.3)	6 (0.4)	800/827 (96.7)	543/572 (94.9)	.09
Median triglycerides (IQR) – mmol/L	1.50 (1.10–2.08)	298 (17.9)	1.23 (0.97–1.52)	2.07 (1.69–2.68)	<.001
Median HDL cholesterol (IQR) – mmol/L	1.10 (0.90–1.30)	305 (18.3)	1.20 (1.01–1.49)	0.93 (0.80–1.10)	<.001
Median BMI (IQR) – kg/m²	26.1 (24.0–29.0)	17 (1.0)	25.00 (23.03–27.12)	28.67 (25.71–31.52)	<.001

Data are give as *n* (%), mean ± SD, or median (interquartile range [IQR]) unless stated otherwise.

BMI = body mass index; CVA = cerebrovascular accident; HDL = high density lipoprotein; IQR = interquartile range; MetS = metabolic syndrome; TIA = transient ischaemic attack.  
\* Including 263 cases in which MetS could not be defined because of missing data.

**Table 2** Components of metabolic syndrome in patients with or without metabolic syndrome (MetS) studied for occurrence of restenosis after carotid endarterectomy

alt-text: Table 2					
Component	All patients* ( <i>n</i> = 1668)	Missing <i>n</i> (%)	No-MetS <i>n</i> (%)	MetS <i>n</i> (%)	<i>p</i>

	<i>n</i> (%)				
Serum triglycerides >1.69 mmol/L	546 (32.7)	298 (17.9)	129/813 (15.9)	414/553 (74.9)	<.001
Serum HDL cholesterol <1.03/1.29 mmol/L	689 (41.3)	305 (18.3)	255/810 (31.5)	432/552 (78.3)	<.001
BMI (>30 kg/m²)	310 (18.6)	15 (0.9)	39/827 (4.7)	244/569 (42.9)	<.001
Hypertension	1487 (89.1)	23 (1.4)	679/817 (83.1)	559/572 (97.7)	<.001
Elevated blood glucose	469 (28.1)	3 (0.2)	90/830 (10.8)	318/572 (55.6)	<.001

Data are given as *n* (%). BMI = body mass index; HDL = high density lipoprotein; MetS = metabolic syndrome.

\* Including 263 cases in which MetS could not be defined because of missing data.

Most patients (73.0%) had surgery for a symptomatic carotid stenosis (Table 3). No statistically significant differences were found in patient symptoms between no-MetS and MetS patients. In addition, most patients had a high grade (70-99%) carotid stenosis with no differences in the degree of stenosis between groups (*p* = .425).

**Table 3** Symptomology and degree of carotid restenosis in patients with or without metabolic syndrome (MetS) after carotid endarterectomy

alt-text: Table 3

Carotid stenosis	All patients* ( <i>n</i> = 1668) <i>n</i> (%)	Missing <i>n</i> (%)	No-MetS ( <i>n</i> = 831) <i>n</i> (%)	MetS ( <i>n</i> = 574) <i>n</i> (%)	<i>p</i>
<i>Symptomatic carotid stenosis</i> (%)	1217 (73.0)		623/831 (75.0)	419/574 (73.0)	.41
Ocular	242 (14.5)		125/831 (15.0)	80/574 (13.9)	.56
TIA	488 (29.3)		248/831 (29.8)	160/574 (27.9)	.42
CVA	446 (26.7)		234/831 (28.2)	162/574 (28.2)	.98
Miscellaneous†	41 (2.5)		16/831 (1.9)	17/574 (3.0)	.21
<i>Ipsilateral pre-operative stenosis</i> (%)		6 (0.4)			.43
0–49%	8 (0.5)		6/831 (0.7)	1/572 (0.2)	.25
50–69%	156 (9.4)		82/831 (9.9)	56/572 (9.8)	.96
70–99%	1498 (89.8)		743/831 (89.4)	515/572 (90.0)	.71

Data are given as *n* (%). CVA = cerebrovascular accident; MetS = metabolic syndrome; TIA = transient ischaemic attack.

\* Including 263 cases in which MetS could not be defined because of missing data.

† Miscellaneous = carotid endarterectomy for vertebrobasilar insufficiency or haemodynamic impairment causing watershed TIA/CVA.

## MetS and restenosis

The median follow up period was 26.4 months (interquartile range [IQR] 12.3–55.2). For MetS these numbers were 26.2 months (IQR 12.8–52.9). For no-MetS these numbers were 27.4 months (IQR 12.6–57.9).

During follow up, 68 restenoses (8.2%) occurred in the no-Mets group and 58 (10.1%) in the MetS group (*p* = .44) (Table 4). A total of 22 re-interventions were performed for a restenosis. A redo endarterectomy was performed in 12 cases (six in the no-MetS group, three in the MetS group, and three in the group in which MetS could not be defined), and a carotid artery stenting procedure was performed in 10 cases (five in the no-MetS group and five in the MetS group).

**Table 4** Carotid restenosis\* and absolute number (%) of events at different timepoints after carotid endarterectomy in patients with or without metabolic syndrome (MetS)

alt-text: Table 4

Group	Patients <i>n</i>	3 mo	1 y	2 y	3 y	4 y	5 y	6 y	7 y	8 y	9 y
<i>All patients</i> <sup>†</sup>	1668										
Interval		84 (5.0)	45 (2.7)	8 (0.5)	6 (0.4)	3 (0.2)	6 (0.4)	2 (0.1)	3 (0.2)	1 (0.1)	2 (0.1)
Cumulative		84 (5.0)	129 (7.7)	137 (8.2)	143 (8.6)	146 (8.8)	152 (9.1)	154 (9.2)	157 (9.4)	158 (9.5)	160 (9.6)
<i>No-MetS</i>	831										
Interval		37 (4.5)	19 (2.3)	3 (0.4)	1 (0.1)	2 (0.2)	3 (0.4)	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)
Cumulative		37 (4.5)	56 (6.7)	59 (7.1)	60 (7.2)	62 (7.5)	65 (7.8)	66 (7.9)	67 (8.1)	67 (8.1)	68 (8.2)
<i>MetS</i>	574										
Interval		30 (5.2)	17 (3.0)	3 (0.5)	4 (0.7)	1 (0.2)	2 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cumulative		30 (5.2)	47 (8.2)	50 (8.7)	54 (9.4)	55 (9.6)	57 (9.9)	57 (9.9)	58 (10.1)	58 (10.1)	58 (10.1)

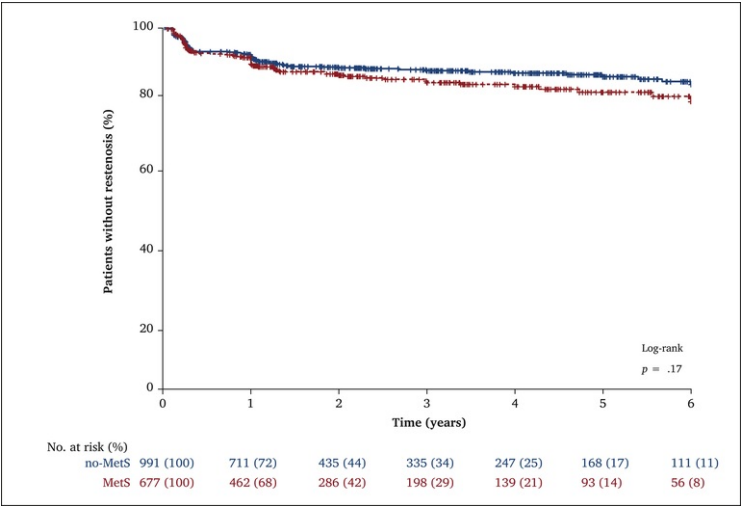
Data are given as *n* (%) unless stated otherwise.

MetS = metabolic syndrome.

\* Restenosis defined as degree of stenosis ≥ 50%.

<sup>†</sup> Including 263 cases in which MetS could not be defined because of missing data.

Using the multiply imputed data sets, the unadjusted hazard ratio (HR) for developing restenosis was 1.12 (95% confidence interval [CI], 1.00-1.25; *p* = .049). Fig. 1 illustrates the Kaplan-Meier estimate of freedom from restenosis. In the adjusted analysis, the HR for estimate of freedom from restenosis in the no-MetS group vs. the MetS group was 1.10 (95% CI 0.98-1.23; *p* = .10).



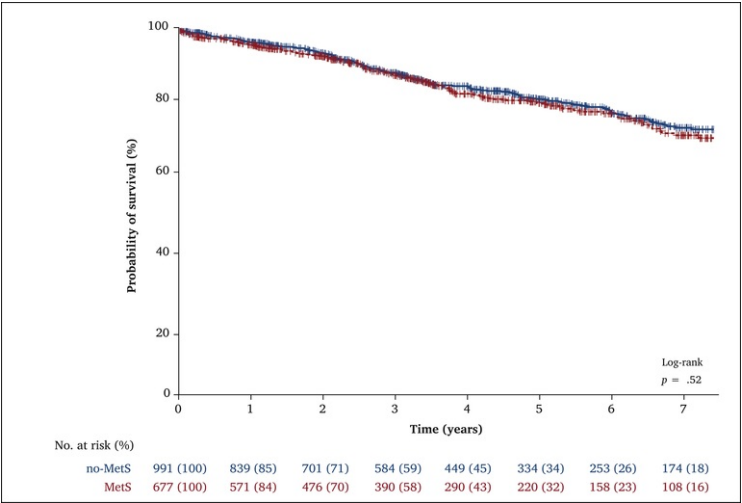
**Figure 1** Cumulative Kaplan-Meier estimate of freedom from restenosis after carotid endarterectomy between patients without or with metabolic syndrome (no-MetS and MetS, respectively), after imputation of missing data. MetS = metabolic syndrome.

alt-text: Figure 1

## MetS and patient survival

During follow up, 308 patients died: 178 patients in the no-MetS group and 130 in the MetS group. The unadjusted HR for all cause mortality was 1.10 (95% CI 0.87-1.40; *p* = .43) using the multiply imputed data sets. In the

adjusted analysis, the HR for death in the no-MetS compared with the MetS group was 1.20 (95% CI 0.94-1.54;  $p = .14$ ). [Fig. 2](#) illustrates the Kaplan-Meier mortality curve.



**Figure 2** Cumulative Kaplan-Meier estimate of probability of survival after carotid endarterectomy between patients without or with metabolic syndrome (no-MetS and MetS, respectively), after imputation of missing data. MetS = metabolic syndrome.

alt-text: Figure 2

## Discussion

This study, the largest published cohort so far, shows that MetS has little clinical relevance in advanced atherosclerotic carotid disease with regard to restenosis and death. This is in line with previous findings that MetS has no influence on short and long term outcomes after CEA.<sup>5</sup>

The influence of MetS on various cardiovascular mechanisms and diseases remains unclear. The identification of predisposing factors associated with the incidence of restenosis has been the focus of great interest and debate. Hypercholesterolaemia and hyperlipidaemia, diabetes mellitus, hypertension, and obesity all have been found to have a role in plaque destabilisation and recurrent stenosis.<sup>27,28</sup>

Because MetS patients are subject to a number of atherosclerotic risk factors, specific atherosclerotic processes will probably be more profound in MetS patients. There is also a suggestion that the combination of factors constituting MetS can synergistically impact atherosclerotic carotid disease, for example by amplifying the LDL cholesterol associated increases in carotid intima-media thickness. LDL cholesterol is also associated with carotid stenosis by itself, but it is not part of MetS.<sup>29,30</sup> The relative contribution of the separate components constituting MetS (and the cut off points used) to the process of atherosclerosis will differ. For this study, the international definition of MetS was adhered to.

A recent meta-analysis showed that common carotid intima-media thickness was increased in patients with MetS compared with no-MetS patients with a higher prevalence of plaque formation. The authors concluded that this finding is consistent with the view of MetS as a cluster of haemodynamic and non-haemodynamic factors promoting vascular hypertrophy and plaque formation.<sup>31</sup> Still, the consistency of the risk factors clustered in MetS as a predictor for future events is complex. A large European cohort study found that the prevalence and prognostic significance of MetS differed according to age and sex, making the contribution of MetS even more complex.<sup>32</sup>

It appears that in carotid artery disease, MetS contributes mainly to the initiation and progression of atherosclerosis in the early stages.<sup>33-35</sup> This is supported by the observation in a murine model that development of intimal hyperplasia is markedly different in diabetes mellitus and MetS compared with controls.<sup>36</sup>

In a cohort of 148 patients with an asymptomatic carotid plaque (using duplex ultrasound with computer assisted analysis), MetS did not affect the stenosis grade or lead to more unstable carotid plaques.<sup>37</sup> Because MetS may be a predictor for development of atherosclerosis, its role as clinical predictor in the more advanced stages of atherosclerosis may be less contributory.<sup>34,38</sup> Contradictory clinical outcomes have been reported in other diseases and interventions. For instance, MetS appears not to be associated with clinical restenosis after percutaneous coronary intervention. In patients requiring arteriovenous fistulas, lower cumulative patency rates and worse survival is reported when MetS is present.<sup>3,39</sup> For the carotid artery, MetS had previously been found to be an independent predictor for restenosis after CEA, warranting more frequent and/or long term surveillance.<sup>8</sup> That study however, consisted only of a small number of patients ( $n = 79$ ), with a selected population including only men with a much higher incidence of MetS. Another factor that may contribute to contradicting results in the various studies is the



proportion of patients put on best medical treatment (BMT), and their compliance with the prescribed medication. An increase of statin use from 17% to 70% has been described in the enrolment era (1993–2003) of a large carotid surgery trial (ACST). In that trial, the stroke rate in the BMT group was 5.1%, more than half that in a trial from the 1990s (ACAS).<sup>40–42</sup>

In the present cohort, all patients were (if not already) put on antiplatelet, statin, and antihypertensive medication. Compliance with the medication, and changes in prescribed medication over time unfortunately were not recorded in the registries.

This study shows that MetS is not a risk factor for restenosis after carotid endarterectomy. At present, in the guideline Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS),<sup>16</sup> the presence of metabolic syndrome in a patient with atherosclerotic carotid artery disease is not part of the decision making for carotid surgery. The present authors advise using the ESVS guideline to decide whether or not there is an indication for carotid endarterectomy. Nonetheless, it is believed that this study contributes to an answer in the ongoing dilemma regarding restenosis in MetS patients after carotid endarterectomy.

This study has a few limitations that must be addressed. It is a retrospective analysis of a prospectively collected database, which entails the risk of selection bias. Even though MetS played no part in selecting patients for CEA, certain comorbid conditions may nevertheless have led to the initial patient selection. Also, MetS criteria were missing in 15.8% (263 of 1668) of the included patients and could no longer be determined retrospectively. Statistical analyses of data sets with missing data yields less precise estimates and, more importantly, may lead to biased inferences. To overcome these problems, the method of multiple imputation was used. Multiple imputation involves generating multiple values for each missing observation based on information from the available data (i.e., producing estimates similar to those analysed from full data). The analyses of multiply imputed data take into account the uncertainty in the imputations, producing accurate standard errors. Although the present results are based on the largest cohort on MetS and CEA published to date, an even larger cohort could give a different outcome. This applies to both restenosis and death. Finally, despite the outcome of the present study, conflicting findings have been published. Pooling data could help in obtaining sufficient power and heterogeneity. After a comprehensive literature review, the number of suitable studies (based on methodology and quality) was deemed too low to perform a formal meta-analysis to be added to this paper. In conclusion, MetS is useful in the screening and detection of the early stages of atherosclerosis but appears to play no role in the risk assessment of restenosis after carotid surgery.

## Conflict of interest

None.

## Funding

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## Queries and Answers

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